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Review

Drug-induced Brugada syndrome

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ABSTRACT

Brugada syndrome (BrS) is an inherited cardiac disorder that is associated with an electrocardiogram pattern of ST segment elevation on right precordial leads and a high incidence of sudden death. Diagnosis requires documentation of a coved-type ST segment that occurs spontaneously or in the presence of a class IA or IC antiarrhythmic agent. A wide variety of other drugs, including antianginals, antidepressants, antipsychotics, and antihistamines, have been reported to unmask or induce the electrocardiographic and arrhythmic manifestations of BrS. This review focuses on drug-induced BrS phenotypes, prevalence, and underlying mechanisms.

Contents

1. Introduction

Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome that is associated with ST segment elevation on right precordial leads and a relatively high incidence of sudden cardiac death. BrS is characterized by an electrocardiogram (ECG) pattern manifesting as prominent J waves, giving the appearance of an ST segment elevation in the right precordial leads on an ECG. Diagnostic criteria require the presence of a coved-type ST segment elevation with a J point elevation ≥2 mV [1].

The BrS ECG is often widely dynamic, with ST segment elevations that fluctuate from hour to hour, day to day, and month to month. Diurnal variation shows that events occur more frequently at night during periods of high vagal tone [2]. In some patients, the

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use of frequent ECGs or 12-lead ambulatory Holter monitoring is useful for diagnosing BrS.

The concealed BrS phenotype can be unmasked using class IA and IC antiarrhythmic drugs, which possess potent use-dependent sodium channel blocking activity [3]. These drugs induce or exaggerate the appearance of a coved-type ST with J point elevation (type 1 BrS ECG) and can convert type 2 to type 3 ST segment elevations to type 1 (coved-type) elevations. Pilsicainide (Japan), procainamide (USA), ajmaline (Europe), and flecainide (Europe) have all demonstrated good efficacy in unmasking BrS and have become valuable tools for the diagnosis of BrS [4,5].

In addition to antiarrhythmic drugs, a wide variety of other drugs have been reported to unmask or induce the ECG and arrhythmic manifestations of BrS, including antianginals, antidepressants, antipsychotics, and antihistamines (Table 1). Postema et al. recently created a website that tracks drugs that are capable of causing adverse events in patients with BrS (w w w.brugadadrugs.org) [6].

BrS has been associated with mutations in 12 different genes. More than 300 mutations in *SCN5A* ($Na_v1.5$, BrS1) have been reported in 11–28% of BrS probands [7–9]. Mutations in *CACNA1C* ($Ca_v1.2$, BrS3), *CACNB2b* ($Ca_v\beta2b$, BrS4), and *CACNA2D1* ($Ca_v\alpha2\delta$, BrS9) are found in approximately 13% of probands [10,11]. Mutations in the glycerol-3-phosphate dehydrogenase 1-like enzyme gene (*GPD1L*, BrS2), the β_1-subunit of Na channel (*SCN1B*, BrS5) *KCNE3* (MiRP2, BrS6), the β3-subunit of Na channel (*SCN3B*, BrS7) *KCNJ8* (BrS8), *KCND3* (BrS10), *MOG1* (BrS11), and *SLMAP* (BrS12) are more rare [12–19]. Mutations in these genes lead to a loss of function in sodium channel current (I_{Na}) and calcium channel current (I_{Ca}) as well as a gain of function in the transient outward potassium current (I_{to}) or adenosine triphosphate (ATP)-sensitive potassium current ($I_{K\text{-}ATP}$).

Acquired forms of the BrS mimic some forms of the congenital syndrome by reducing I_{Na} and I_{Ca} and by augmenting I_{to} and $I_{K\text{-}ATP}$.

Table 1
Drugs that can cause the Brugada phenotype.

1. Antiarrhythmic drugs
Sodium channel blockers
Class IC drugs (pilsicainide, flecainide, propafenone)
Class IA drugs (ajmaline, procainamide, disopyramide, cibenzoline)
Class III drugs (amiodarone)
Calcium channel blockers (verapamil)
Beta-blockers (propranolol intoxication)
2 Antianginal drugs
Calcium channel blockers (nifedipine, diltiazem)
Potassium channel opener (nicorandil)
3 Psychotropic drugs
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine)
Phenothiazine
Selective serotonin reuptake inhibitors (fluoxetine)
Lithium
Anticonvulsants (oxcarbazepine, clonazepam)
Antipsychotics (trifluoperazine, loxapine)
4 Other drugs
Anesthetics (bupivacaine, propofol)
Histaminic H1 receptor antagonists
Acetylcholine, edrophonium
Cocaine
Alcohol

2. Antiarrhythmic drugs

2.1. Sodium and calcium channel blockers (class IC and IA drugs)

Approximately one-fourth of cases of BrS are caused by a loss-of-function mutation in *SCN5A*. Mutations in *SCN5A* (BrS1) has been identified in 11–28% of BrS probands [9]. *SCNB1* (BrS5), *SCN3B* (BrS7), *MOG1* (BrS11), and *SLMAP* (BrS12) are relatively rare. These mutations are all associated with a loss of function of sodium channel current that gives rise to a BrS phenotype. Likewise, agents that reduce I_{Na} give rise to BrS phenotypes, in most cases by unmasking a congenital form of the syndrome.

Pharmacologic challenge by several sodium channel blockers is an established tool for the diagnosis of BrS. Sodium channel blockers such as pilsicainide, ajmaline, and flecainide are capable of inducing ST segment elevations and unmasking a concealed BrS phenotype.

Pilsicainide is a class I sodium channel blocker antiarrhythmic drug that is used principally in Japan. Its primary indication is for the treatment of atrial tachyarrhythmias, including atrial fibrillation. Fig. 1 shows the results of a pilsicainide challenge in a case of BrS. Pilsicainide was given intravenously at a dose of 1.0 mg/kg over 10 min. After administration, the J point and ST segment are elevated and display a coved-type or type I ST segment elevation. Sodium channel blockers can unmask a type I ST segment elevation or convert a type 2 (saddleback) ST segment elevation to a type 1 BrS pattern, as in this case.

Late potentials (LP) in signal-averaged electrocardiograms (SAECG) have been reported to correlate with the unmasking of a coved-type (type 1) ST segment elevation by pilsicainide [20]. Fig. 2 shows the SAECG before and after pilsicainide administration in a BrS case. The SAECG was normal in controls but displayed LP after pilsicainide administration. LP are traditionally thought to be due to delayed activation of the myocardium, but in the case of BrS has been suggested to be the result of accentuation of abnormal repolarization (delayed second upstroke of the epicardial action potential [AP] and concealed phase 2 reentry) in the region of the right ventricular outflow tract (RVOT) [21].

Pilsicainide, as well as other sodium channel blockers, including propafenone and flecainide, can cause the appearance of a BrS ECG when it is routinely used for the treatment of atrial fibrillation. Wolpert et al. compared the effects of intravenous flecainide and ajmaline with respect to their ability to induce or accentuate the typical ECG pattern of BrS [22]. A coved-type ST segment elevation in the right precordial leads was induced or enhanced in 22 of 22 patients following ajmaline administration but in only 15 patients in response to flecainide. The authors presented evidence in support of the hypothesis that greater inhibition of I_{to} by flecainide renders it less effective. Blockage of I_{to} counters the effect of the drug and causes an outward shift of the balance of current activity during the early phases of the AP.

To our knowledge, there are no data relative to pilsicainide blockage of I_{to}. Pilsicainide may be the most powerful agent for unmasking BrS, although a direct comparison between ajmaline [23] and pilsicainide [24] is not available.

2.2. Calcium channel blockers (verapamil)

Mutations in *CACNAC1C* (BrS3), *CACNB2b* (BrS4), and *CACNA2D1* (BrS9) have been associated with BrS in approximately 13% probands [10,11]. Experimental models have shown that verapamil accentuates the epicardial AP notch and produces the BrS phenotype [25]. Fish et al. reported that the use of a combination sodium and calcium channel block may be more effective than the use of a sodium channel blocker alone in causing the BrS phenotype [26]. In clinical cases, verapamil was reported to cause ST segment elevation and permit the induction of programmed electrical stimulation-induced VT/VF in a case of BrS [27].

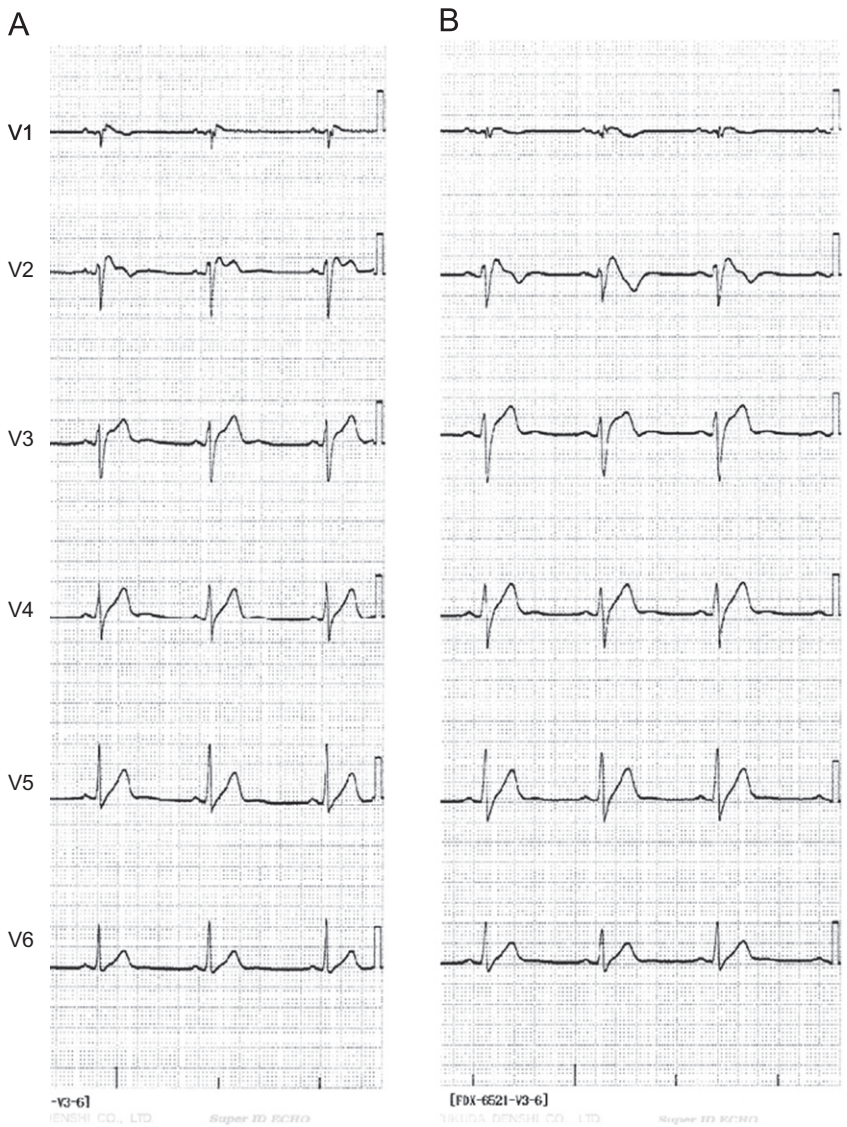

Fig. 1. Electrocardiographic recordings in a pilsicainide challenge test in a patient with Brugada syndrome. (A) At baseline, a saddleback-type ST segment (type 2) is present in the right precordial leads. (B) Intravenous administration of pilsicainide (50 mg) converts type 2 ST segment elevation to a coved-type ST segment (type 1), thus unmasking the Brugada syndrome phenotype.

2.3. Beta-blockers

Because β-adrenergic agonists such as isoproterenol (ISO) exert ameliorative effects on BrS, β-adrenergic blockers may exert a pro-arrhythmic effect. Propranolol, a non-selective β1-adrenergic agent, was reported to cause the BrS pattern on ECG during intoxication [28]. It is noteworthy that high concentrations of propranolol can inhibit I_{Na}, leading to the outward shift of the current active during phases 1 and 2 [28].

3. Antianginal drugs

3.1. ATP-sensitive potassium channel opener

ATP-sensitive potassium channels are found in the heart, pancreas, smooth muscles, skeletal muscles, brain, and kidneys. K_{ATP} channels consist of four pore-forming Kir6.x subunits and four regulatory ATP-sensing sulfonylurea receptor (SURx) subunits. Kir6.2/Kir6.1 is encoded by *KCNJ11*/*KCNJ8*, respectively, while SUR2A/SUR1 is encoded by *ABCC9*/*ABCC8*, respectively. $I_{K\text{-}ATP}$ agonists such as nicorandil exert their antianginal actions by causing vasodilation and improving coronary blood flow.

Mutations in *KCNJ8* (BrS8), the gene encoding Kir6.1, and *ABCC9*, the gene encoding the ATP-sensing subunit *SUR2A* (BrS12), have been reported to cause a gain of function of $I_{K\text{-}ATP}$, and thus contribute to the development of a BrS phenotype [15,29]. The K_{ATP} channel is activated by a reduction of intracellular ATP. This appears to be more readily achieved in the epicardium than in the endocardium [30]. Miyoshi et al. showed a greater induction of $I_{K\text{-}ATP}$ in the epicardium in response to ischemia and suggested that it was due to either a lower threshold for activation or a denser distribution of K_{ATP} channels or other K^+ channels at the epi layer [31]. Pinacidil, an $I_{K\text{-}ATP}$ channel opener, has been shown to induce the BrS phenotype in experimental models of BrS [32,33].

There are only few case reports of the BrS phenotype being induced by antianginal drugs alone. However, a combination of nifedipine and isosorbide dinitrate (ISDN) has been reported to induce a BrS phenotype [34]. Cases of coexistent vasospastic angina and BrS [35] have also been reported. Acetylcholine-induced coronary vasospasm has likewise been reported to cause

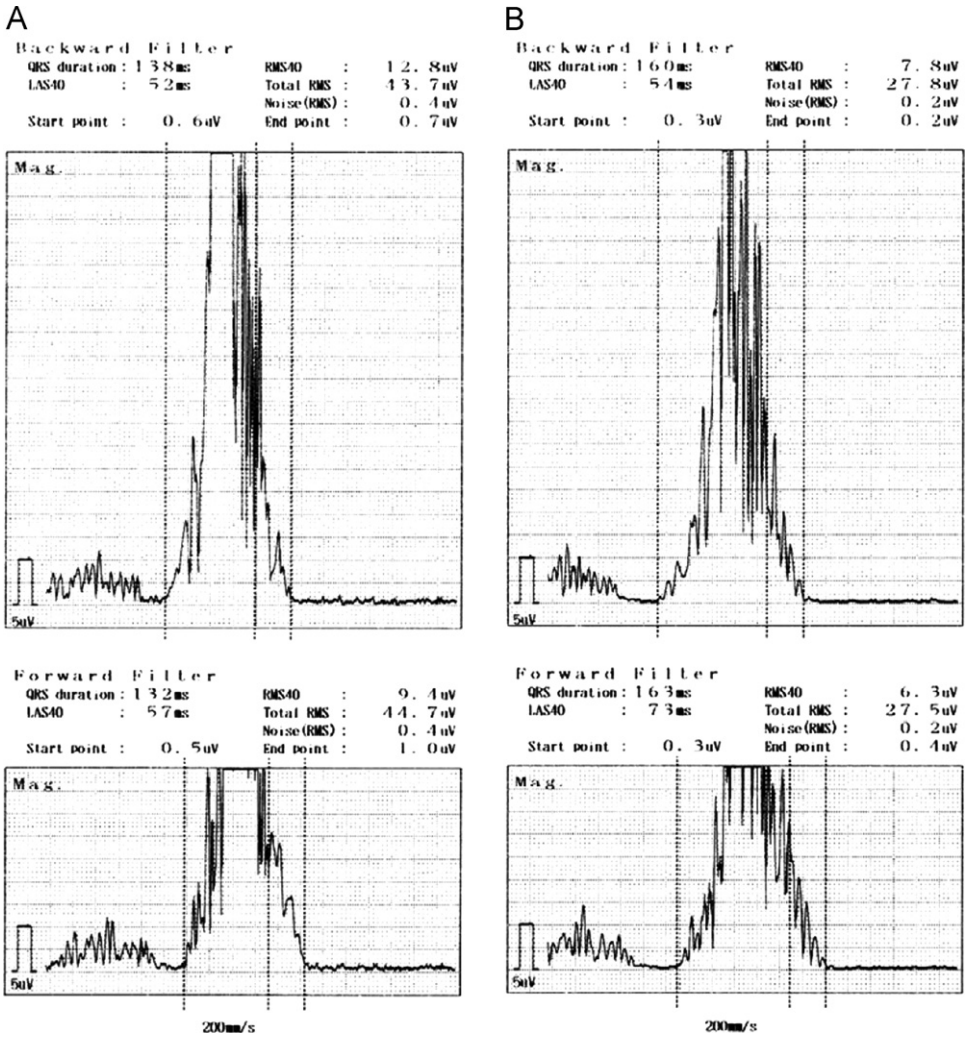

Fig. 2. Signal-averaged electrocardiogram (SAECG) before and after the intravenous administration of pilsicainide in a BrS case. (A) In controls, SAECG was normal with no late potential manifests. (B) Intravenous administration of pilsicainide (50 mg) induced the appearance of late potential (filtered-QRS was prolonged [138 ms vs. 160 ms] and root-mean square voltage was reduced [12.8 μV vs. 7.8 μs]).

a BrS pattern on ECG [36,37]; however, the coexistence of coronary vasospasm and BrS is rare.

4. Psychotropic drugs

4.1. Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and clomipramine)

Psychotropic drugs are well recognized to induce cardiac arrhythmias and can cause an ST segment elevation consistent with BrS [38]. Tricyclic antidepressants have been reported to induce the BrS pattern on ECG over a wide range of antidepressant dosages [39]. Amitriptyline, a tricyclic antidepressant, has recently been reported to induce the BrS phenotype in clinics [40–43] as well as in an experimental model [44]. Amitriptyline was shown to cause an outward shift in the balance of current activity during the early phases of the epicardial AP by reducing the peak sodium channel current.

Figs. 3 and 4 show that the effect of amitriptyline in the reduction of I_{Na} and induction of the BrS phenotype in a right ventricular wedge with NS5806 (I_{to} agonist) caused loss of the AP dome in Epi2 and led to phase 2 reentry and polymorphic ventricular tachycardia (VT). Amitriptyline alone did not induce any arrhythmias, suggesting that amitriptyline-induced inhibition of I_{Na} unmasks the Brugada ECG phenotype and facilitates the development of an arrhythmogenic substrate only in the setting of a genetic predisposition by creating repolarization heterogeneities that give rise to phase 2 reentry and VT. Amitriptyline can also block I_{to} [45], explaining why it fails to induce the BrS phenotype even at high concentrations (1 mM). The effect of tricyclic antidepressants for blocking I_{Na} has been documented in several studies [46,47]. Amitriptyline has also been reported to prolong the QT interval because of its ability to block I_{Kr} [48].

5. Lithium

Lithium is widely used to treat depression and bipolar disorder. The lithium-induced BrS phenotype is not common, but it can be observed even with use of therapeutic dosages [49]. Lithium also causes other conduction dysfunctions such as sinus node dysfunction, conduction block, and ventricular arrhythmias. Lithium has also been shown to block I_{Na} in a dose-dependent manner [50].

6. Selective serotonin reuptake inhibitors

Data regarding the selective serotonin reuptake inhibitor (SSRI)-induced BrS phenotype are scarce. Paroxetine and fluvoxamine have

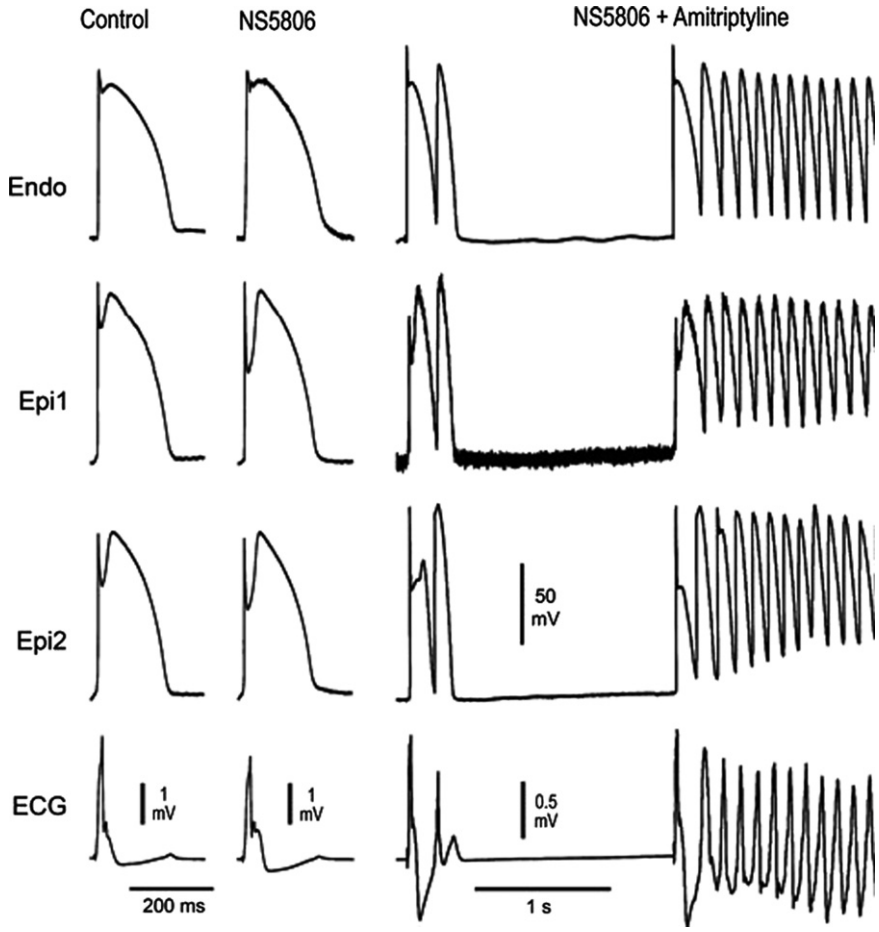

Fig. 3. Amitriptyline-induced Brugada phenotype in a coronary-perfused right ventricular wedge preparation. Action potentials (APs) recorded from an endocardial and two epicardial sites, together with a pseudo-electrocardiogram (ECG). The transient outward potassium current agonist leads to the accentuation of the epicardial AP notch and J wave in the ECG. Amitriptyline in the presence of NS5806 induces the Brugada ECG phenotype and polymorphic ventricular tachycardia. NS5806, transient outward potassium channel current agonist. (Modified from Minoura and Antzelevitch [44] with permission.)

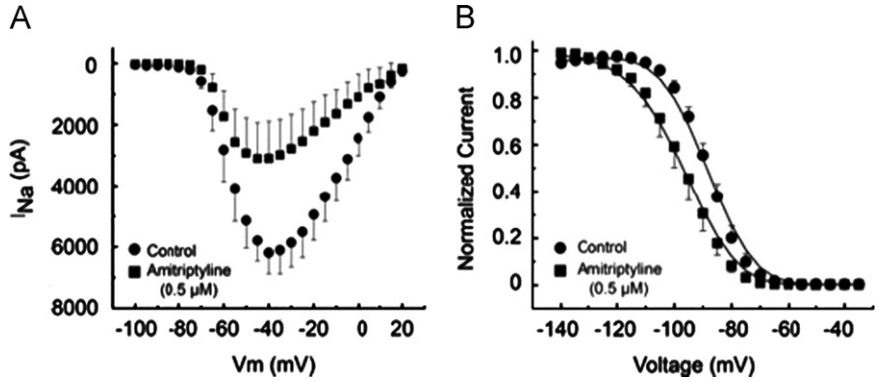

Fig. 4. Amitriptyline blocks the sodium channel current in TSA201 cells transfected with *SCN5A* and *SCN1B*. (A) Amitriptyline blocks peak I_{Na} at +20 mV ($P < 0.01$). (B) Steady-state inactivation curve. Amitriptyline shifts the half-inactivation potential by −20 mV ($P < 0.01$). TSA201 cells, a transformed human kidney cell line; NS5806, a transient outward potassium channel current agonist. (Modified from Minoura and Antzelevitch [44] with permission.)

been shown to lead to a BrS pattern in the ECG via a reduction in I_{Na} [51,52].

7. Anticonvulsant and antipsychotics

Phenytoin is an antiepileptic agent. There are case reports of BrS caused by supratherapeutic phenytoin levels in a patient with a seizure disorder [53]. There are several reports of ECG signs of BrS in cases of hyperkalemia in conjunction with psychotropic drug overdoses, notably phenothiazines [54].

8. Anesthesia

Anesthetics such as propofol and bupivacaine are commonly used in clinical settings. Bupivacaine was reported to induce the BrS phenotype in silent carriers of an *SCN5A* mutation [55].

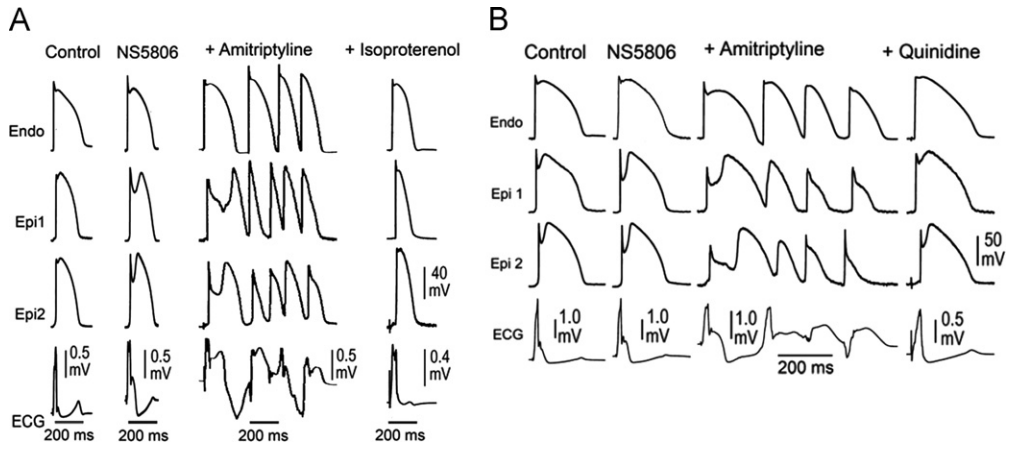

Fig. 5. Effect of isoproterenol and quinidine in the suppression of Brugada syndrome induced by amitriptyline in a coronary-perfused right ventricular wedge preparation. Action potentials (APs) recorded from one endocardial and two epicardial sites together with a pseudo-electrocardiogram (ECG). (A) and (B) show traces recorded in controls, after NS5806 (8 μM) administration, and after further addition of amitriptyline (0.2 μM). Amitriptyline accentuated the AP notch and the J wave, leading to phase 2 reentry and polymorphic ventricular tachycardia (pVT). The addition of isoproterenol or quinidine restored the AP dome and suppressed the pVT. NS5806, transient outward potassium channel current agonist. (Modified from Minoura and Antzelevitch [44] with permission.)

Another report also demonstrated a bupivacaine-induced BrS phenotype that normalized following drug withdrawal.

Propofol has been reported to cause sudden cardiac death in one non-genetic and 6 unclear cases [56]. Propofol has been shown to inhibit neuronal sodium channels [57], but there are no data relative to cardiac sodium channels. It is unclear whether a genetic predisposition is present in those who display a BrS phenotype after propofol administration.

9. Other drugs

Overdose of diphenhydramine (an H1 histamine receptor antagonist) is reported to induce a BrS phenotype [58,59]. Antihistamines are known to cause QT prolongation secondary to I_{Kr} inhibition. Cocaine is known to block the sodium channels and thus to unmask a BrS phenotype [60]. Alcohol intoxication is also reported to induce a BrS phenotype [61]. Interestingly, a full stomach after a large meal is known to induce a BrS phenotype [62]. This response it believed to be due to increased parasympathetic tone. Any agent capable of producing an outward shift in the balance of current during the early phases of the epicardial AP is expected to be capable of creating or unmasking a BrS phenotype.

10. Mechanism underlying drug-induced BrS

Our working hypothesis regarding the mechanisms underlying induction of the drug-induced BrS phenotype is that these drugs produce an outward shift in the balance of current activity during the early phases of the epicardial AP, similar to the mechanism underlying the development of congenital BrS. Th is can be accomplished either by inhibition or reduction of depolarizing inward currents such as I_{Na} or I_{Ca} or augmentation of a repolarizing outward current such as I_{to} [25].

The outward shift of net current leads to the accentuation of the epicardial AP notch, which in turn causes loss of the AP dome in the right ventricular (RV) epicardium. The loss of the dome results in both epicardial and transmural dispersion of repolarization, which gives rise to an ST segment elevation and creates a vulnerable period within the RV wall. The epicardial dispersion of repolarization can result in phase 2 reentry, thus creating a closely coupled premature beat capable of capturing the vulnerable window and precipitating polymorphic VT [1,63,64].

BrS is a right ventricular disease because I_{to} is most prominent in the right ventricle. I_{to} is also much more prominent in the epicardium than in the endocardium, which is responsible for the prominent AP notch in the epicardium but not the endocardium. This heterogeneous distribution of I_{to} and the AP notch is responsible for inscription of the J wave [65].

Recent studies have proposed that delayed conduction in the RVOT is responsible for some cases of BrS [66,67]. A debate of the repolarization vs. depolarization hypothesis for BrS is the subject of a point counterpoint published in 2010 [68].

11. Treatment for the drug-induced BrS

Drug withdrawal is an effective treatment strategy in most cases of drug-induced BrS. In those cases in which additional measures are necessary, therapy is aimed at rebalancing the current activity during the early phases of the epicardial AP, either by increasing I_{Ca} or reducing I_{to}. The increase in I_{Ca} can be achieved with the administration of ISO, which is especially effective in suppressing drug-induced VF storms in BrS cases in the emergency room. ISO can also effectively suppress VF in drug-induced BrS. I_{Ca} augmentation can also be achieved with the phosphodiesterase III inhibitor, cilostazol. The reduction of I_{to} is best achieved using quinidine. Fig. 5 illustrates the ability of quinidine and ISO to suppress the BrS phenotype in experimental models of BrS. Quinidine also blocks I_{Na}, I_{Kr}, and I_{Ks} at therapeutic plasma levels, but its usefulness for the treatment of BrS is well established both in experimental studies and clinical cases [69].

Conflicts of interest

The authors have no conflicts of interest to disclose.

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